Energy Metabolism and Mitochondria

**Date:** September 2, 2005 *
**Time:** 9:40 am - 10:30 am *
**Room:** G-202 Biomolecular Building
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*Please consult the online schedule for this course for the definitive date and time for this lecture.

**Office Hours:** By appointment

**Assigned Reading:** This syllabus.

**Lecture Objectives:** To understand the basic concepts of energy metabolism in cells and to learn about the central function of mitochondria in this process. This lecture will focus on the following:

1) Overview of Energy Metabolism: Glycolysis, TCA Cycle  
2) Mitochondrial Structure: ATP Synthesis by Oxidative Phosphorylation  
3) Mitochondrial Genetics: Mitochondrial DNA, Mitochondrial Diseases

The syllabus is meant to accompany the lecture presentation. All material is considered important to your understanding of the subject.
I. All living cells require energy to carry out various cellular activities. This energy is stored in the chemical bonds of organic molecules (e.g., carbohydrates, fats, proteins) that we eat as food. These organic molecules are broken down by enzymatic reactions in cells to generate energy in the form of adenosine triphosphate (ATP). The ATP generated by these pathways in cells is used to drive fundamental cellular processes such as cell division, cell motility, cell differentiation, cell signaling, organelle movement, etc.

II. **Multiple Stages of Cellular Metabolism:**

a) **Overview:**

The food we consume is mainly comprised of proteins, polysaccharides (carbohydrates) and fats. These are first broken down into smaller units: proteins into amino acids, polysaccharides into sugars, and fats into fatty acids and glycerol. This process of digestion occurs outside the cell.

The amino acids, simple sugars and fatty acids then enter the cell and undergo oxidation by glycolysis (in the cytosol) and the citric acid cycle (in the mitochondria) to generate ATP (from ADP and P).

b) **Glycolysis:**

During glycolysis, each molecule of glucose is converted into two molecules of pyruvate, generating two molecules of NADH (nicotinamide adenine dinucleotide) and two molecules of ATP in the process.

Glycolysis produces ATP without molecular oxygen. It takes place in the cytosol of cells, and is the major source of energy for anaerobic microorganisms.

In aerobic cells, the pyruvate that is generated during glycolysis is metabolized further in the mitochondria by the citric acid cycle and the electron transport chain to generate additional ATP. In anaerobic organisms or under anaerobic conditions (where oxygen is limiting), this pyruvate is converted into ethanol and CO$_2$ (e.g. in yeast) or into lactate (e.g. in muscle).

c) **Citric Acid Cycle (Tricarboxylic acid cycle, Krebs cycle):**

In aerobic organisms, most of the ATP is produced via the citric acid cycle and the process of oxidative phosphorylation. This process occurs in the mitochondria and is dependent on molecular oxygen. In addition to generating ATP (one
A molecule of glucose generates 30 molecules of ATP, these reactions also produce CO\(_2\) and H\(_2\)O.

The pyruvate produced during glycolysis enters mitochondria where it is converted to acetyl CoA. Likewise, fatty acids are also converted to acetyl CoA via the fatty acyl CoA intermediate.

Acetyl CoA molecules are a major source of energy for aerobic organisms. These enter the citric acid cycle to combine with oxaloacetate, and through several steps, generate 3 NADH, 2 FADH\(_2\), and 1 GTP molecules.

The majority of ATP is generated when the NADH and FADH\(_2\) molecules transfer their electrons via the electron transport chain. This generates a proton gradient that is then used to produce ATP. This entire process is called oxidative phosphorylation.

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**Figure 1.** An overview of cellular metabolism

### II. Cellular Storage of Energy:

Since cells require a constant supply of ATP, but have only periodic access to food, they have the ability to convert sugars and fats for storage.

For short-term storage, sugars are stored in the form of glycogen, which is present as small granules in the cytoplasm of many cells (*e.g.* liver and muscle). When needed, glycogen can be readily converted back to glucose-1-phosphate, which then enters glycolysis.

Fatty acids are the best source of energy for long-term storage. These are stored as fat droplets (triacylglycerols) in fat cells, also known as adipocytes. When needed, these cells release fatty acids into the bloodstream that is then taken up by other cells and converted into acetyl CoA. Acetyl CoA then enters the citric acid cycle and generates ATP.
IV. Mitochondrial Structure:

The mitochondria are highly dynamic organelles that are essential for the majority of ATP generation in eukaryotic cells.

Mitochondria contain an outer and an inner membrane, with an intermembrane space (between the inner and outer membrane) and an internal matrix.

The outer mitochondrial membrane contains channels (comprised of porins) that make the membrane permeable to molecules of less than 10 kDa molecular weight.

In contrast, the inner mitochondrial membrane is particularly impermeable to molecules due to the high proportion of cardiolipin in the membrane. It has a high protein content (75 %), including transport proteins that make the membrane selectively permeable. The components of the electron transport chain are embedded in the inner membrane (one exception to this is cytochrome c, which is present in the intermembrane space). The inner membrane is also packed in a folded conformation, called cristae, that substantially increases the surface area of the inner membrane in the mitochondria.

The mitochondrial matrix contains several enzymes including those involved in the citric acid cycle. The matrix also contains mitochondrial DNA and the mitochondrial protein synthesis machinery.

V. ATP Synthesis (Oxidative Phosphorylation/Chemiosmotic Theory):

The process of glycolysis and citric acid cycle generates high-energy electrons that are carried by the NADH and FADH$_2$ molecules.

The NADH (and FADH$_2$) molecules transfer their electrons via multiple electron carriers that are components of the electron transport chain. These are located in the mitochondrial inner membrane. The electrons that are transferred along the chain ultimately reduce molecular oxygen to produce water.

Importantly, the transfer of electrons along the electron transport chain is coupled to the movement of protons (H$^+$) from the matrix side to the intermembrane space. This generates a pH and a voltage gradient across the inner membrane that ultimately drives ATP synthesis via the F$_1$F$_0$ ATPase.

The F$_1$F$_0$ ATPase is a multisubunit protein complex located in the inner mitochondrial membrane. The movement of protons (H$^+$) back to the matrix through this protein complex drives a “rotor” that promotes the synthesis of ATP from ADP and P$_i$. 

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Thus, the impermeability of mitochondrial inner membrane is critical for ATP generation. Agents that permeabilise the inner membrane disrupt mitochondrial ATP generation.

The ATP generated in the matrix is then transported to the outside of the mitochondria for exchange with ADP, thus keeping the cycle going. This ATP is used to drive all cellular metabolic functions.

Typically, cells maintain a high ATP/ADP ratio (of about 10) and inhibitors of the electron transport chain (e.g. cyanide) that block ATP synthesis are highly toxic to organisms.

![Overview of ATP synthesis by oxidative phosphorylation](image)

**Figure 2. Overview of ATP synthesis by oxidative phosphorylation**

### VI. Genetics of Mitochondria:

It is generally accepted that mitochondria evolved from bacteria that were engulfed by nucleated ancestral cells.

Although mitochondria contain their own genetic material, the mitochondrial DNA is relatively small (about 16 kb) and encodes only a small subset of molecules (13 proteins, 2 rRNAs, 22 tRNAs) that are needed for its function. The remaining components of the mitochondria are encoded by the nucleus.

Mitochondrial DNA is double-stranded, circular, is not associated with histones, and has a different codon usage than nuclear DNA (e.g. UGA= Tryptophan). It is located in the mitochondrial matrix.
Mitochondria are very dynamic. They change their shape and size (through the process of fusion and fission) frequently in cells according to cellular needs and environment.

Mitochondria are propagated in cells by division (fission). Therefore, these are largely inherited maternally (because the egg supplies most of the cytoplasm for the zygote) in a non-mendelian manner.

Mitochondrial DNAs have a relatively high rate of mutations and are therefore highly divergent in evolution.

Defects in mitochondrial function underlie many human degenerative diseases. Specific mitochondrial mutations are associated with many human diseases, including Leber’s hereditary optic neuropathy (LHON) disease, Kearns-Sayre syndrome (KSS) and MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes). Importantly, tissues that have a high energy requirement (e.g. brain, heart, muscle) are particularly vulnerable to mitochondrial dysfunction.

Additional Reading:

